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Detection of urinary macrophages expressing the CD16 (FcγRIII) molecule: A novel marker of acute inflammatory glomerular injury

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Detection of urinary macrophages expressing the CD16 (FcγRIII) molecule: A novel marker of acute inflammatory glomerular injury.

Background. The CD16 antigen is the Fcγ receptor III. CD14+CD16+ cells are proinflammatory monocytes/macrophages (Mo/MΦ) that constitute a minor population in the peripheral blood of healthy individuals. Little is known about the expression of CD16 antigen on Mo/MΦ in glomerulonephritis.

Methods. Flow cytometric analyses were performed on urine and blood samples obtained from 209 patients with various renal diseases. Patients variously suffered from rapidly progressive crescentic glomerulonephritis (RPGN), membranoproliferative glomerulonephritis (MPGN), postinfectious acute glomerulonephritis (AGN), Henoch-Schönlein purpura nephritis (HSPN), IgA nephropathy (IgAN), membranous nephropathy (MN), minimal change nephrotic syndrome (MCNS), lupus nephritis (LN), acute interstitial nephritis, hereditary nephropathy, idiopathic renal hematuria (IRH), and renal stone.

Results. The CD16+ MΦ population of cells was present in the urine of hematuria-positive patients with proliferative glomerulonephritis, including AGN, IgAN, RPGN, MPGN, and LN with acute inflammatory lesions, such as endocapillary proliferation, tuft necrosis, and cellular crescents. In contrast, the urinary CD16+ MΦ population was negligible in hematuria-positive patients with nonproliferative renal disease, including hereditary nephropathy, IRH, and renal stone and also in patients with proliferative glomerulonephritis lacking acute inflammatory lesions. Total urinary MΦ of these patients were much less than those of patients having proliferative glomerulonephritis with acute inflammatory lesions. Transient expansion of the CD16+ MΦ population in urine was observed during the acute exacerbation of urinary abnormalities, whereas the disappearance of CD16+ MΦ closely preceded the amelioration of urinary abnormalities in patients with proliferative glomerulonephritis. In 38 of the 98 patients positive for CD16+ MΦ population in urine, the CD16+ Mo population was negligible in peripheral blood. Immunohistochemically, CD16+ MΦ were present in the glomeruli of active proliferative glomerulonephritis, whereas such cells were absent in inactive proliferative glomerulonephritis or nonproliferative glomerular diseases.

Conclusion. CD16+ MΦ may be effector cells involved in the acute inflammation common to all types of proliferative glomerulonephritis. Furthermore, the detection of CD16+ MΦ in urine, as well as urinary MΦ counts, may serve as a useful indicator of the active stage of proliferative glomerulonephritis.

Key words: glomerulonephritis, inflammation, flow cytometry, necrosis, cellular crescents.

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Macrophages (MΦ) are readily identified in the glomerulus in most forms of proliferative glomerulonephritis, particularly rapidly progressive glomerulonephritis. Flow cytometry (FCM) is a powerful tool for precisely examining the characteristics of cells, including mononuclear cells in the urine of patients with proliferative glomerulonephritis. Unlike examination by renal biopsy, this method is noninvasive and thus facilitates serial examination. Using FCM, we previously found and reported that the magnitude of urinary MΦ excretion is significantly correlated with the extent of crescentic lesions in biopsy specimens [1, 2]. In the course of a phenotypical analysis of urinary MΦ using FCM, we found that there was a urinary MΦ subset that expressed CD16 antigen (a human natural killer cell antigen) [3] in certain patients. The CD16+ Mo is regarded as a proinflammatory monocyte (Mo), and the CD16+ Mo population is increased in the peripheral blood of patients suffering from disorders such as sepsis [3] and malignancy [4]. The purpose of this study was to clarify the possible clinical diagnostic utility of the expression of CD16 antigen on the MΦ detected in the urine of patients afflicted with proliferative glomerular disorders.

METHODS

Patients and urine samples

Peripheral blood and freshly voided urine samples (50 to 100 ml) were obtained from 20 healthy individuals and 204 patients with various types of glomerular disease: IgA nephropathy (IgAN, $N = 94$), Henoch-Schönlein purpura nephritis (HSPN, $N = 10$), idiopathic renal hematuria (IRH, histologically confirmed as "isolated C3 deposition disease," $N = 17$) [2], crescentic rapidly progressive glomerulonephritis (RPGN, $N = 17$), membranoproliferative glomerulonephritis (MPGN, $N = 9$), lupus nephritis (LN, $N = 11$), postinfectious acute glomerulonephritis (AGN, $N = 16$), minimal change nephrotic syndrome (MCNS, $N = 7$), membranous nephropathy (MN, $N = 9$), hereditary nephropathy ($N = 9$), and acute interstitial nephritis (AIN, $N = 5$). Urine samples were also obtained from five patients with kidney stones exhibiting macroscopic hematuria. In 15 patients with MPGN, crescentic IgAN, RPGN, HSPN, and LN, serial FCM analyses were performed. In addition, urine samples were obtained serially from five patients with IgAN both in the clinical quiescence phase and acute exacerbation phase following pharyngitis.

Flow cytometric analysis

Urine samples were centrifuged for 10 minutes at 1500 r.p.m. The sediment was washed three times in phosphate-buffered saline (PBS) and was resuspended. The viability of the mononuclear cells in urine was 95 to 99% by Trypan blue dye exclusion. Fifty microliters of the cell suspensions were transferred to small test tubes. Ten microliters of green (FITC)-labeled or red (PE)-labeled monoclonal antibody were added, and the suspension was gently mixed and incubated at 4°C for 30 minutes. After incubation, the cells were washed twice in PBS. Then 1 ml of IMMUNO-LYSE solution (Coulter, Hialeah, FL, USA) was added to each tube for hemolysis. After the tubes had been allowed to sit for 30 seconds, 150 μl of fixative (Coulter) was added. The cells were then washed three times with 3 ml of PBS and were analyzed by FCM. The combinations of antibodies used were FITC-labeled anti-CD14 (Leu M3, mouse IgG2b; macrophages/monocytes; Becton Dickinson, San Jose, CA, USA) and PE-labeled anti-CD16 (Leu 11c, mouse IgG1; IgG Fc receptor III; Becton Dickinson), or PE-labeled anti-CD3 (Leu 4, mouse IgG1; Pan T cells; Becton Dickinson). Simultest Control (IgG1-FITC + IgG2a-PE; Becton Dickinson) was used as a negative control.

The flow cytometric analysis was carried on a FACScan (Becton Dickinson). Twenty thousand cells were analyzed in each sample. Consort 30 (Becton Dickinson) software was used to analyze the data. For each cell, four parameters were measured simultaneously: forward scatter (FSC), indicating cell-volume; side scatter (SSC), indicating cell-structure; FITC; and PE. The selection of cells for fluorescence analysis was performed within a scattergram using Paint-A-Gate (Becton Dickinson) software, providing an objective means of excluding debris and other cells from the lymphocyte and monocyte gate [2]. Briefly, the localization of CD3+ and CD14+ cells in the scattergram (FSC vs. SSC) was optimized using the Paint-A-Gate program. Then the gate was set on the cells in which these two cell subpopulations were included. The percentage and number of a specific leukocyte subset were determined by two-color FCM. In a two-color analysis of urine samples with the combination of anti-CD14 and anti-CD16 antibodies, when the CD16+ MΦ subset was present, a part of the CD16+ MΦ overlapped the cluster of cell debris, which made it difficult to accurately count the number of CD16+ MΦ in the cytogram (Fig. 1). Thus, in the FCM analyses for urine, the presence of CD16+ MΦ was defined when the cluster of CD16+ MΦ, usually partly overlapping the cluster of cell debris, was present on a two-color cytogram. In addition, quantitative MΦ concentrations in urine were determined by two-color FCM analysis, with the combination of anti-CD14 and anti-CD3 antibodies as described previously [2].

The definition of "active stage" in this study was based on the presence of acute inflammatory lesions, such as cellular crescent, tuft necrosis, and/or endocapillary proliferation in the biopsy specimens.

Immunohistochemical study

Kidney biopsy specimens from various forms of glomerulonephritis (IgAN with active lesions, $N = 7$; IgAN without active lesions, $N = 7$; RPGN, $N = 3$; MPGN, $N = 4$; LN, $N = 3$; MN, $N = 7$; MCNS, $N = 4$; hereditary nephropathy, $N = 3$) were assessed by immnohistochemical study. Specimens for the immunohistochemical study were fixed in periodate-lysine-2% paraformaldehyde at 4°C for six hours and were washed in PBS containing increasing concentrations of sucrose. Then they were embedded in OCT compound (Miles Pharmaceutical, Napervill, IL, USA) and were rapidly frozen. Frozen sections (4 μm thick) were cut in a cryostat and overlaid onto egg albumin-coated glass slides. Histofine kit (Nichirei, Tokyo, Japan) was used for the immunohistochemical study. Briefly, the procedure involved successive incubation with the primary antibody (3G8/FcγRIII Coulter, diluted at 1:50) for 12 hours at 4°C. Endogenous peroxidase was inactivated by incubation with 100% methanol containing 0.3% hydrogen peroxide. After being washed with PBS and incubated in Streptavidin enzyme conjugated for 30 minutes at room temperature, the reaction products were visualized by incubation with 0.025% diaminobenzidine (DAB) solution containing 0.01 M sodium azide and 0.006% hydrogen peroxide and counter stained with methyl green.

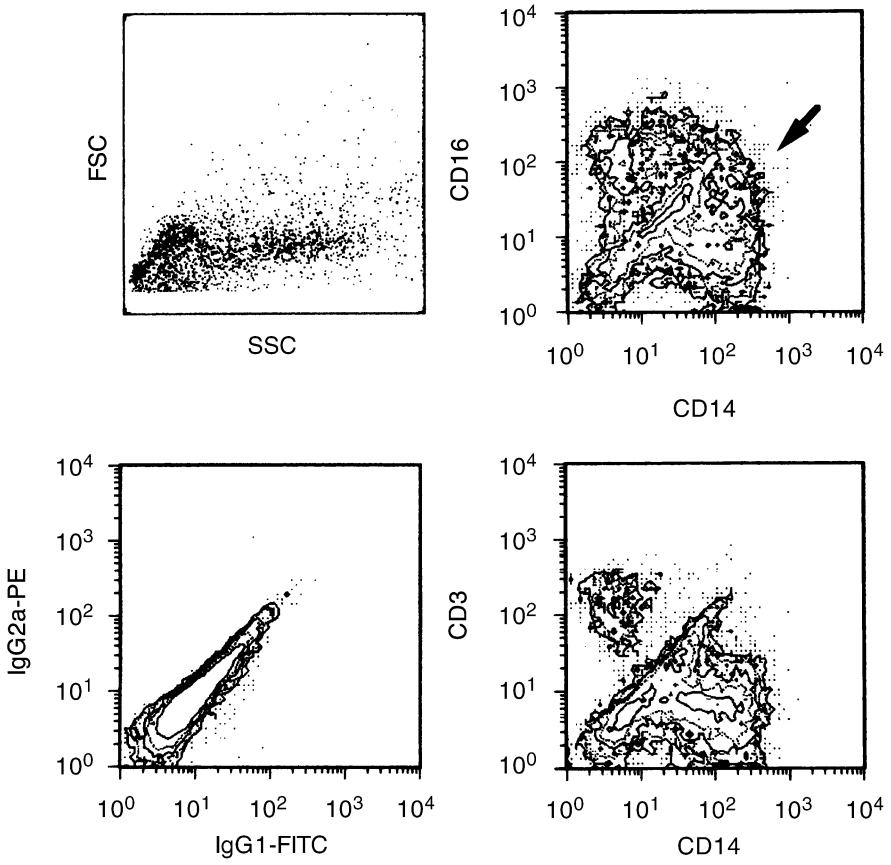

Fig. 1. Two-color flow cytometric analysis of urinary mononuclear cells of a patient with rapidly progressive crescentic glomerulonephritis (RPGN). CD16+ MΦ were present in the urine (arrow). In two-color flow cytometric analysis using anti-CD14+ and anti-CD3+ antibody, there was no double-positive cell population.

To obtain precise information about infiltrating CD16+ cells in the glomerulus, we used immunoelectron microscopy sections according to the method described previously [5]. Briefly, cryostat sections adjacent to those taken for light microscopy were treated by the indirect immunoperoxidase method. After incubation with the first antibody for 24 hours at 4°C, the sections were combined with F(ab)2 fragments of goat antimouse IgG labeled with horseradish peroxidase (diluted at 1: 100 in PBS; Amersham Japan Co., Tokyo, Japan) overnight for the second antibody. The sections were fixed in 1% glutaraldehyde for 20 minutes at room temperature. After washing, they were incubated with 0.025% DAB solution containing 0.006% hydrogen peroxide for two to five minutes. They were then post-fixed with 2% osmium tetroxide for 45 minutes at room temperature, dehydrated in graded ethanol, and embedded in Epon. Ultrathin sections were examined with an electron microscope.

RESULTS

Expression of CD16 antigen on urinary macrophages

In normal subjects and hematuria-negative patients, urinary MΦ counts were negligible, and no CD16+ MΦ were detected. CD16 antigen expression was marked on urinary MΦ in most patients with RPGN and AGN, whereas the expression of CD16 antigen on urinary MΦ was negligible in patients with IRH, hereditary N, MN, MCNS, or renal stones. In IgAN, HSPN, MPGN, and LN patients, the CD16+ MΦ were present in those having acute inflammatory lesions such as endocapillary proliferation, cellular crescents, and/or necrotizing lesions. In contrast, CD16+ MΦ were negligible in patients without such active lesions (Fig. 2).

Expression of CD16 antigen on monocytes in peripheral blood

In normal subjects, CD16 antigen was only rarely expressed on monocytes (Mo) in peripheral blood (ranged from 0 to 8% of the entire Mo population). In patients with primary renal parenchymal disease, there was a significant increase in the proportion of CD16+ Mo. A total of 12 of 17 patients with RPGN, 6 of 9 with MPGN, 38 of 94 with IgAN, 4 of 10 with HSPN, and 9 of 19 with AGN showed a significant increase in the proportion of CD16+ Mo (more than 10% of the entire Mo population). In all six patients with AGN in whom the FCM analysis was carried out within 10 days after the clinical

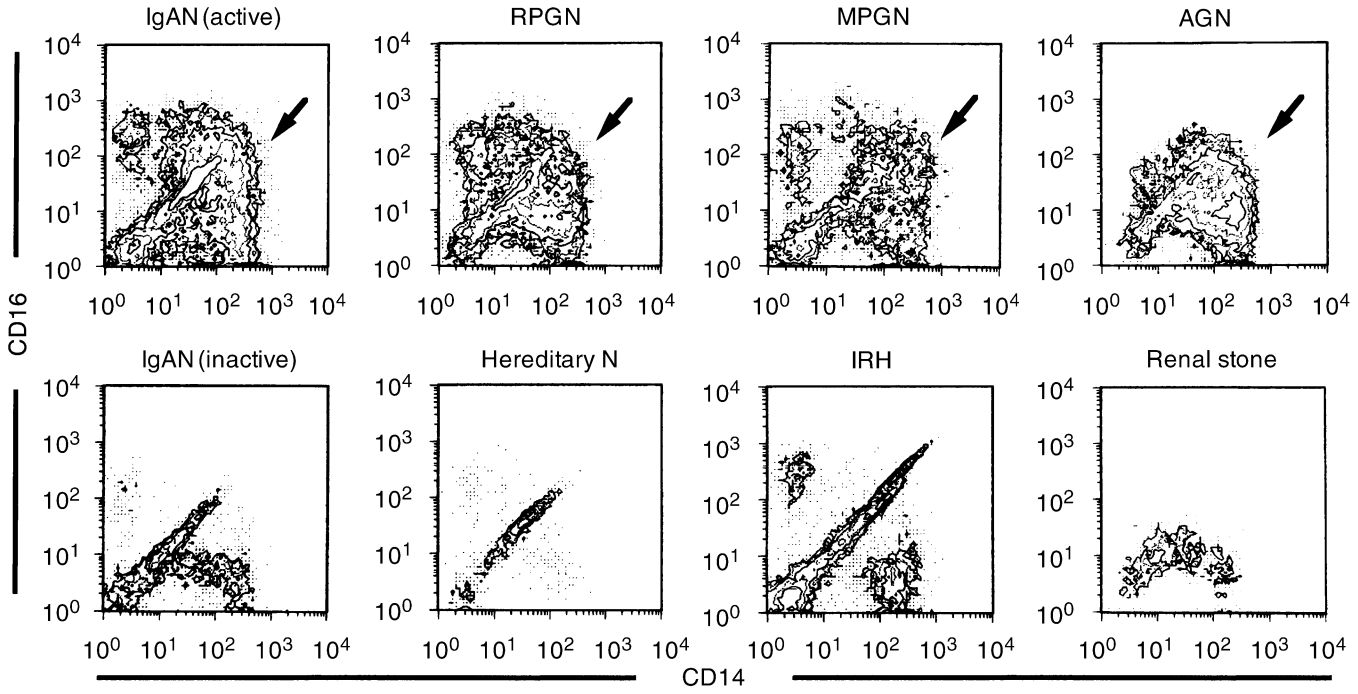

Fig. 2. Two-color flow cytometric analysis of urinary mononuclear cells obtained from patients with various renal diseases. CD16+ MΦ are present in urine during the active phase of proliferative glomerulonephritis, regardless of the disease type (arrow). There are no CD16+ MΦ in the urine of patients with nonproliferative glomerular diseases and renal stone. Abbreviations are: AGN, postinfectious acute glomerulonephritis; IgAN, IgA nephropathy; IRH, idiopathic renal hematuria; MPGN, membranoproliferative glomerulonephritis; RPGN, rapidly progressive glomerulonephritis.

onset, both urinary CD16+ MΦ and an increased CD16+ Mo population in peripheral blood were observed. Among patients with nonproliferative glomerulopathy, 4 of 9 with MN exhibited increases in the proportion of CD16+ Mo. In contrast, in patients with MCNS, IRH, and hereditary nephropathy, there were no significant increases in the proportion of the CD16+ Mo, except for one patient with hereditary nephropathy. In approximately 40% (38/98) of the patients who exhibited a CD16+ MΦ population in urine, the percentage of CD16+ Mo in peripheral blood was within normal levels (Table 1). None of these patients with elevated CD16+ Mo in peripheral blood had any signs of sepsis or clinically detectable infectious disease. At the time of examination, none of the 16 patients with AGN had persistent symptoms of preceding infection, such as acute tonsillitis.

The clinical setting and CD16+ Mo/MΦ

In patients with AGN, both CD16+ Mo in peripheral blood and CD16+ MΦ in the urine disappeared with the amelioration of glomerulonephritis, and the disappearance of CD16+ MΦ and decrease in urinary MΦ counts closely preceded the amelioration of urinary abnormalities (Fig. 3). In five IgAN patients, urine FCM analyses were carried out both in the clinical quiescence phase and transient acute exacerbation phase following pharyngitis. CD16+ MΦ were negligible in the urine in the clinical quiescence phase, whereas the cluster of CD16+ MΦ transiently appeared concomitantly with a marked increase in the total MΦ counts in the urine in the acute exacerbation phase (Fig. 4).

The proportion of CD16+ MΦ in the urine of patients with crescentic IgAN, HSPN, RPGN, MPGN, and LN diminished remarkably in most of the cases, concomitant with the decline in urinary total MΦ counts in response to steroid therapy (Fig. 5). Again, the disappearance of CD16+ MΦ closely preceded the amelioration of urinary abnormalities.

Immunohistochemical study

CD16+ cells were virtually absent in biopsy specimens of nonproliferative glomerular diseases, including MN, MCNS and hereditary nephropathy and IgAN without active lesions. In contrast, in 12 of 17 patients with proliferative glomerulonephritis in the active stage, CD16+ cells were found to be present in the glomerulus (up to 7 positive cells per glomerulus). The glomerular CD16+ cells often showed a polymorphonuclear appearance, suggesting that a considerable proportion of these CD16+ cells were neutrophils, not MΦ.

Immunoelectron microscopic study showed that CD16+ MΦ were present in the glomerular tufts of proliferative GN (Fig. 6).

Table 1. Incidence of CD16+MoMΦ in various renal diseases

		U-CD16+MΦ-positive		U-CD16+MΦ-negative	
	N	PBMo ≥ 10%	<10%	PBMo ≥ 10%	<10%
AGN					
time after onset					
≤10 days	6	6 (100%)	0	0	0
>10 days	10	3 (30%)	6 (60%)	0	1 (10%)
RPGN	17	11 (65%)	4 (24%)	1 (6%)	1 (6%)
HSPN	10	2 (20%)	3 (30%)	2 (20%)	3 (30%)
IgAN	94	28 (30%)	21 (22%)	10 (11%)	35 (37%)
LN	11	3 (27%)	2 (18%)	3 (27%)	3 (27%)
MPGN	9	6 (67%)	2 (22%)	0	1 (11%)
AIN	5	1 (20%)	0	3 (60%)	1 (20%)
MN	9	0	0	4 (44%)	5 (56%)
Hereditary nephropathy	9	0	0	1 (11%)	8 (89%)
IRH	17	0	0	0	17 (100%)
MCNS	7	0	0	0	7 (100%)
Renal stone	5	0	0	0	5 (100%)

Abbreviations are in the **Appendix**.

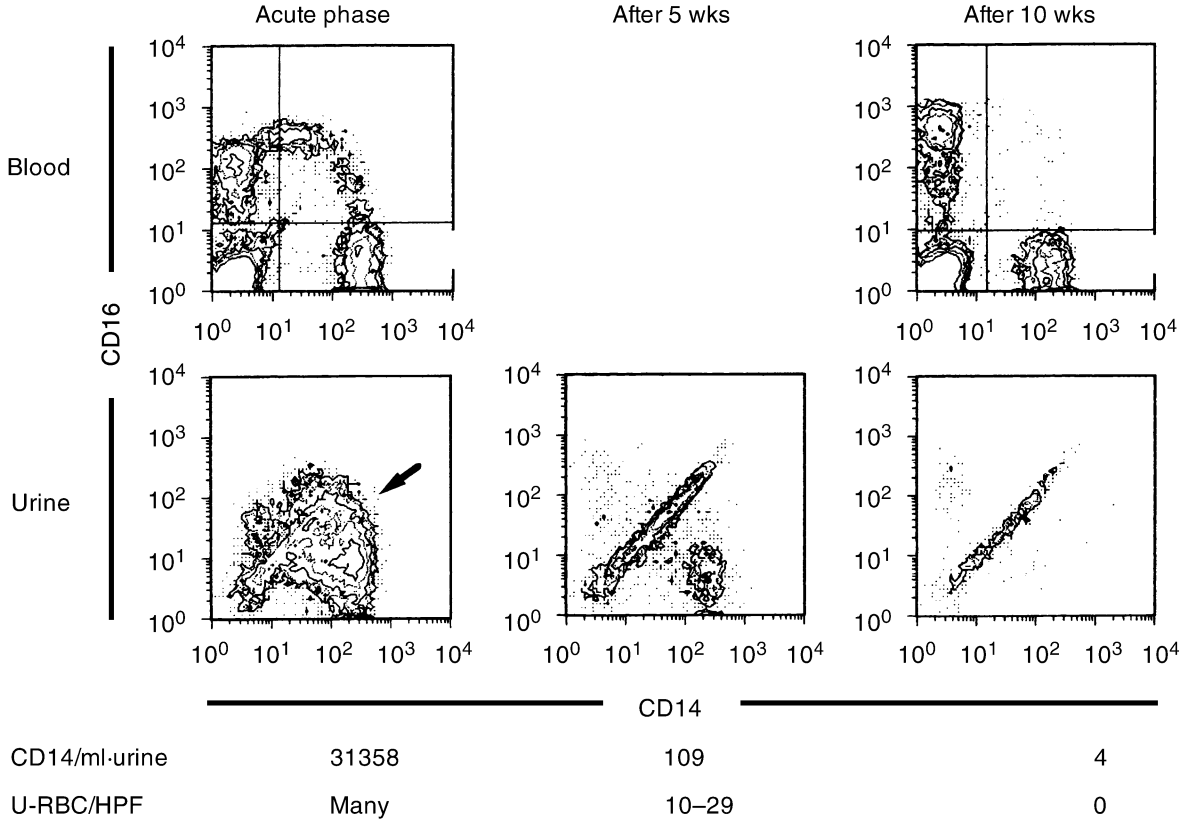

Fig. 3. Serial changes in CD16+ Mo/MΦ in a patient with AGN. Both urinary CD16+ MΦ and CD16+ Mo in peripheral blood disappear with the amelioration of glomerulonephritis.

DISCUSSION

The CD16 antigen has been shown to be the low-affinity IgG receptor, FcγRIII, originally identified on natural killer cells and granulocytes [6, 7]. In the monocytic lineage, CD16 was initially believed to be restricted to a subset of mature MΦ [8], where it apparently plays an important role in phagocytosis [9, 10]. Recently, however, CD16 has also been found on a small subset of circulating monocytes that make up less than 10% of the total Mo population or approximately 1% of all white blood cells [11, 12]. CD16+ Mo have been found to be increased in clinical settings of bacterial sepsis [3], human

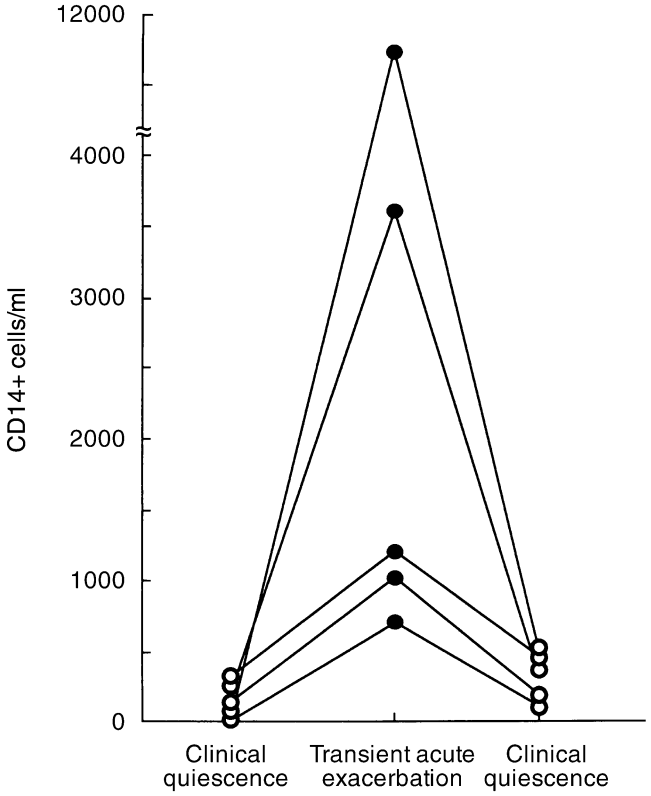

Fig. 4. Serial changes in CD16+ MΦ and MΦ counts in patients with IgAN. A transient expansion of the CD16+ MΦ accompanied by an increase in the total number of urinary MΦ is observed in acute exacerbation phase. Symbols are: (○) CD16+ MΦ-absent; (●) CD16+ MΦ-present.

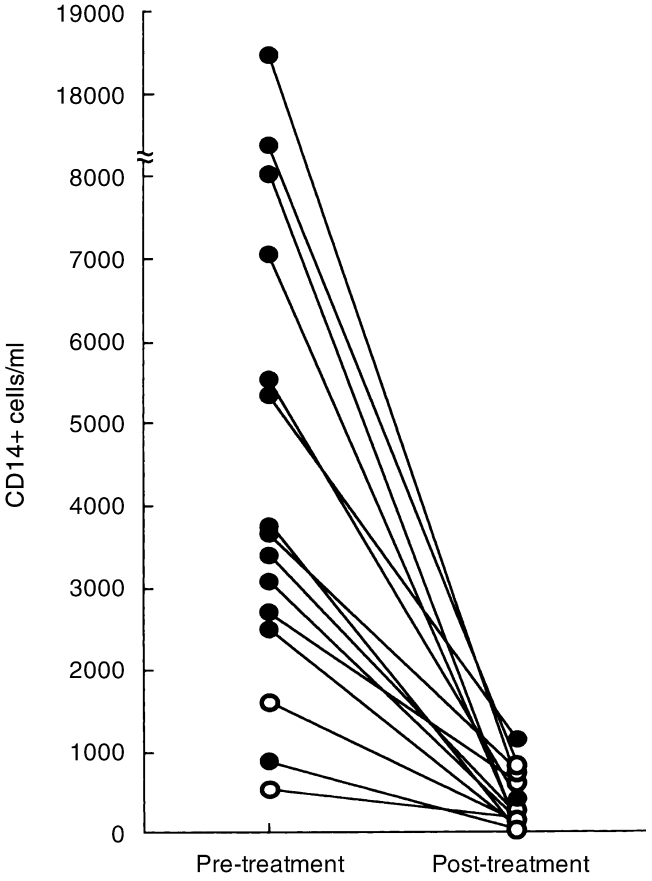

Fig. 5. Serial changes in CD16+ MΦ and MΦ counts in a patient with active glomerulonephritis treated with steroid therapy. The CD16+ MΦ population is lost accompanied by a decrease in total urinary MΦ counts. Symbols are: (○) CD16+ MΦ-absent, (●) CD16+ MΦ-present.

immunodeficiency virus infection [13], and malignancy [4]. Experimentally, a marked increase in the number of CD16+ Mo was observed following the administration of recombinant human MΦ colony-stimulating factor [4, 14].

Our study showed that CD16+ Mo are elevated in the peripheral blood of patients with a variety of glomerular diseases. As there were no clinical signs of systemic bacterial or viral infection and no evidence of malignancies, the patients who exhibited elevated CD16+ Mo in peripheral blood in this study differed clinically from those previously reported. The mechanisms underlying the increase in CD16+ Mo in certain glomerulonephritis patients have yet to be elucidated. However, we hypothesize that subclinical, in some cases nephritogenic, bacterial or viral infection may be involved. In fact, all patients with postinfectious glomerulonephritis in the early stage (within 10 days after the clinical onset) had a significant increase in CD16+ Mo population, and this Mo subset subsequently disappeared from both urine and peripheral blood concurrently with the amelioration of glomerulonephritis. Moreover, chronic tonsillitis is a common finding in patients with IgAN, and the therapeutic effectiveness of tonsillectomy has been reported [15, 16]. Recent studies have suggested a role for *Hemophilus parainfluenzae* as a pathogen of IgAN [17, 18], although clinical symptoms related to this pathogen are rarely observed. Experimentally, bacterial lipopolysaccharide (LPS) enhances CD16 expression on Mo [19]. The mammalian host is continually exposed to environmental indigenous microflora and associated LPS.

As the CD16 antigen is expressed not only on activated Mo/MΦ but also on granulocytes and natural killer cells, granulocytes are likely to be the major subset of CD16+ cells in urinary sediments. Thus, it is practically difficult to recognize CD16+ MΦ in urinary sediments by using conventional immunocytostaining methods under light microscopy. FCM analysis therefore may be a more reliable method for the detection of urinary CD16+ MΦ.

Increased CD16+ MΦ levels in urine were observed in a majority of patients with proliferative glomerulonephritis in the active stage, but in none of the patients with nonproliferative glomerular or urological diseases. Thus, the exposure of MΦ to the urine itself probably does not cause the conversion from CD16– MΦ to

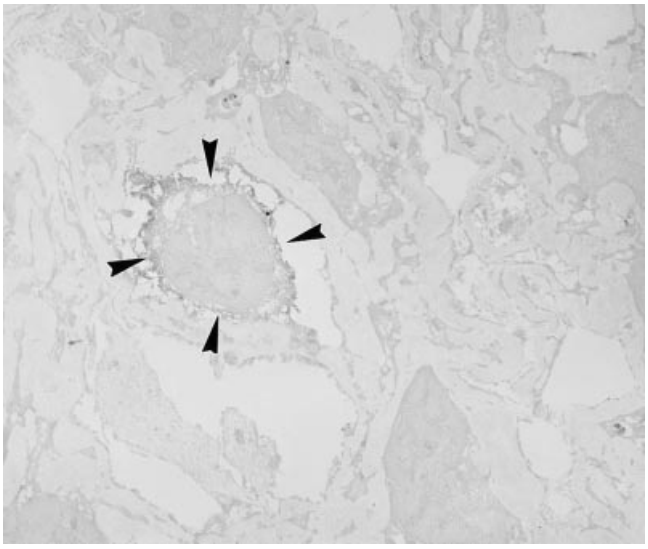

Fig. 6. Immunoelectron micrograph of renal biopsy of a patient with MPGN. CD16+ MΦ is present in the glomerular lumen (arrowheads; original magnification ×3000).

CD16+ MΦ, because if this were the case, nonproliferative disease should also exhibit an increase. It is assumed that the CD16+ MΦ detected in the urine must be converted from CD16– MΦ to CD16+ MΦ either in the circulation or in glomeruli. It is particularly noteworthy that expansion of the CD16+ MΦ population in urine was often observed in patients with proliferative GN even in cases without detectable CD16+ Mo in the peripheral blood. This finding suggests that MΦ activation occurs at acute inflammatory sites in the glomeruli in these patients.

The presence of a CD16+ MΦ population, as well as the increase in total MΦ counts in urine, was well correlated with the level of severity of acute inflammation in the glomeruli. Both the disappearance of the CD16+ MΦ with a decrease in total MΦ counts in the urine and the amelioration of the urinary abnormalities were brought about with steroid therapy in RPGN, HSPN, LN, and IgAN patients, whereas CD16+ MΦ disappeared concurrently with the amelioration of glomerulonephritis in patients with AGN. Furthermore, CD16+ MΦ were detected only in glomeruli in the active phase of proliferative glomerulonephritis and were absent in the inactive phase.

These findings strongly suggest that excretion of CD16+ MΦ may reflect the involvement of CD16+ MΦ in the development of active proliferative glomerular lesions such as cellular crescents, tuft necrosis, and/or endocapillary proliferation, regardless of the type of glomerulonephritis. In other words, in many types of proliferative glomerulonephritis, including RPGN, IgAN, MPGN, AGN, and LN, regardless of the pattern of immunoglobulin deposition in the glomeruli, CD16+ MΦ-related tissue injury is a common event that occurs in the active stage of glomerulonephritis.

Although the functional role of CD16+ Mo/MΦ in proliferative glomerulonephritis has yet to be determined, a recent study demonstrated that CD16+ Mo produced high levels of proinflammatory cytokines such as tumor necrosis factor, whereas the anti-inflammatory cytokines such as interleukin-10 are produced at low levels or are absent, suggesting that these cells may function as efficient immunostimulatory and proinflammatory Mo/MΦ [19]. Thus, it is conceivable that CD16+ MΦ act as proinflammatory cells that trigger an inflammatory immune response in the glomeruli. Furthermore, it has been reported that CD16+ MΦ are cytotoxic to malignant target cells [20, 21]. Whether CD16+ MΦ have such cytotoxic effects on nontransformed glomerular cells must be determined in future studies. From the clinical viewpoint, our study raises the promising possibility that the detection of a CD16+ MΦ population in urine in combination with total urinary MΦ counts using FCM is a useful noninvasive strategy for detecting active proliferative glomerulonephritis.

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APPENDIX

Abbreviations used in this article are: AGN, postinfectious acute glomerulonephritis; AIN, acute interstitial nephritis; FCM, flow cytometry; HSPN, Henoch-Schönlein purpura nephritis; IgAN, IgA nephropathy; IRH, idiopathic renal hematuria; LN, lupus nephritis; MCNS, minimal change nephrotic syndrome; MN, membranous nephropathy; Mo, monocytes; MΦ, macrophages; MPGN, membranoproliferative glomerulonephritis; RPGN, rapidly progressive crescentic glomerulonephritis.

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